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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,964	02/10/2004	Jia-Hwa Fang	PP16502.015	1609

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Alisa Harbin, Esq.  
Chiron Corporation  
Intellectual Property - R440  
P. O. Box 8097  
Emeryville, CA 94662

EXAMINER
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FUBARA, BLESSING M

ART UNIT	PAPER NUMBER
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1618

MAIL DATE	DELIVERY MODE
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05/04/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/775,964	<b>Applicant(s)</b> FANG ET AL.	
	<b>Examiner</b> Blessing M. Fubara	<b>Art Unit</b> 1618	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 16 January 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 34-44 and 58-70 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 34-44 and 58-70 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Examiner acknowledges receipt of request for extension of time, amendment and remarks filed 1/16/07. New claims 68-70 are added. Claims 34, 38-40, 43, 58, 60 and 67 are amended. New claims 62-65 are added. Claims 34-44 and 58-70 are pending.

#### ***Response to Arguments***

**Previous rejections that are not reiterated herein are withdrawn.**

#### ***Claim Rejections - 35 USC § 103***

1. Claims 34-44 and 58-67 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. (US 6,395,253) in view of Paliard et al. (US 6,562,346). New claims 68-70 are included in the rejection. Therefore, claims 34-44 and 58-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. (US 6,395,253) in view of Paliard et al. (US 6,562,346).

LEVY discloses preparation of microspheres that contain DNA or RNA as the bioactive agent (column 4, lines 31, 54 and 55). LEVY prepares a double emulsion of water-in-oil-in-water emulsion by using a condensing agent in one phase and the method comprises the steps of: “(a) dissolving at least one polymer in a water-immiscible organic solvent to yield an organic phase; (b) dissolving a polyanionic bioactive agent in aqueous solution to yield a first aqueous phase; (c) emulsifying the organic and first aqueous phases to yield a first milky emulsion; (d) dissolving a condensing agent in aqueous solution to yield a second aqueous phase; (e) emulsifying the first milky emulsion and the second aqueous phase to yield a second milky emulsion; and (f) removing the organic solvent from the second milky emulsion to yield

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microspheres containing condensed polyanionic bioactive agent with the emulsion meeting claims 34, 35 and 36-39. "The removal of the organic solvent in the final step is preferably by means of evaporation," in one illustrative embodiment (column 4, lines 44 and 45). DNA and RNA are macromolecules and are polynucleotides meeting the requirements of claims 43, 44, 58, 59, 60 and 61. The concept of microspheres meets the microparticle limitation of claims 34, 37, 39, 42, 43, 58, 60, 62, 65-70. Regarding the recitation that the microparticles are not subjected to washing step, it is noted that while the examples in Levy disclose a wash step, the basic preparation disclosed by Levy in section 4.2 does not state a wash step but rather that the microspheres are collected by ultracentrifugation and the alternative protocol disclosed in 4.6. Levy uses 0.1% detergent (SDS in this case). There is no demonstration in applicants' specification that not subjecting the microparticles to a washing step provides unusual/unexpected results to the microparticles. The claims do not recite amount of detergent added to make the microparticle in the emulsion.

Regarding claim 36, which is directed to the process of cross-flow filtration, it is noted that in the cross-flow filtration process of the examined application, four liters of deionized water (Example 5) is used to remove the detergents and this appears to be equivalent to washing so that the cross-filtration step of the claim 34 reads on optional wash step of one of embodiments of Levy at column 13, line 5; at column 18, line 42 (washed with tris-EDTA); at column 20, line 2 (cells washed with PBS buffer). There is also no demonstration that the cross-filtration step performed after removing the organic solvent provides unusual results; Levy discloses filtration as one of the steps. The filtration step in Levy meets the filtration step in claims 34 and 37.

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Regarding the ratio of lactide to glycolide, it is noted that there is no demonstration by applicants that the recited ratio provides unusual/expected results. The silence of Levy on the ratio of lactide to glycolide is an indication that the lactide/glycolide can be used in any desired ratio that would be effective as a condensing agent for the DNA or RNA macromolecules.

Regarding new claims 68-70, Levy in one of the embodiments does not wash the product but removes the solvent from the emulsion by evaporation so that the detergent is not removed or washed off (column 12, lines 58-67).

Levy uses SDS detergent. While Levy does not specifically state the presence of bound detergent in the amounts recited in the claims, it is noted that Levy does not specifically state that the microspheres/particles formed are free of detergent; and it flows from one of the embodiment that does not use a wash step but evaporates off the organic solvent (column 12, lines 58-67) that the detergent is not removed and as such, the microparticles would have detergent associated. However, while Levy teaches SDS and TWEEN, Levy does not disclose the use of cetyl trimethyl ammonium bromide (CTAB) detergent. But Paliard discloses an emulsion that comprises PLG polymer and CTAB (Example 5). Thus Paliard is relied upon for a teaching that the specific CTAB detergent can be used with PLG in an emulsion. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the double emulsion of Levy where the emulsion comprises a detergent and PLG and a solvent. One having ordinary skill in the art would have been motivated to use the CTAB of Paliard in place of SDS with the expectation that the CTAB will interact with the composition to aid the DNA containing microsphere to disrupt to release the DNA.

***Response to Arguments***

2. Applicant's arguments filed 1/16/07 have been fully considered but they are not persuasive.

Applicant argues a) that Levy does not disclose the amounts of bound and unbound detergent claimed. b) that centrifugation is not filtration; c) that cross-flow filtration is not equivalent to washing and that no evidence was provided to support cross-flow being equivalent to washing, that washing and filtration are distinct concepts. d) that Paliard does not cure the deficiency of Levy and that the totality of the references have not been considered.

**Response:**

Regarding a), the examiner agrees with applicant that Levy does not disclose amount of bound or unbound detergent and it was for that reason that a rejection under 35 USC was not made. Rather, Levy does not categorically state that the microspheres produced are free of detergents and furthermore, Levy in one of the embodiments (column 12, lines 58-67) does not employ a wash step. It is also noted that instant claim 36 uses a cross-flow filtration step in which as gleaned from the specification at Example 5, four liters of deionized water is used to remove detergents. Regarding b), it is agreed that centrifugation is not a filtration as pointed to by applicants citing Hawley's Condensed Chemical Dictionary, 14<sup>th</sup> edn., however filtration that collects particles or solids accomplishes the collection of particles or solid by centrifugation and the removal of unwanted components soluble and present in the solvent. The Hawley's condensed dictionary cited by applicant describes filtration as separation of suspended solids from liquids. The main argument in c), is the issue of unbound or bound detergents. In that

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case, it is noted that, Levy does not explicitly disclose that the microspheres are free of detergent and without such equivocation, there is no way to categorically state that the product of Levy is free of detergent. The cross-flow filtration technique used by the instant invention uses 4 liters of deionized water, which is sufficient to lead to washing of the particles. Centrifugation and filtration are both separation techniques (see column 3, lines 57 and 58 of US 5,840,970 to Sumner, Jr. et al.). Regarding d) it is noted that Paliard is relied upon for teaching the use of CTAB with PLGA polymer.

3. Claims 34, 35, 36, 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hagan et al. (US 6,086,901).

O'Hagan discloses the process of preparing an emulsion that comprises poly(lactide-glycolide), solvent and detergent (Example 1); O'Hagan discloses that the size of the droplets (particle, microsphere) depends on the ratio of the detergent to oil (column 12, lines 38-47) and also that water-in-oil-water (w/o/w) type emulsion can be formed of the microparticle (column 10, lines 9-20). The process of claim 36 reads on washing because in the cross-flow filtration process, 4 liters of deionized water (Example 5) are used and the removal of the water appears to approximate the process of filtration/washing. Emulsion and particles meet the emulsion and particle requirements of claims 34, 35 and 43. Claim 42 is a product by process claim and O'Hagan's particles meet the claim. While O'Hagan discloses a washing step, there is no demonstration in applicants' specification that not subjecting the microparticles to a washing step provides unusual/unexpected results to the microparticles. Therefore, it would have been

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obvious to one of ordinary skill in the art at the time the invention was made to prepare microparticle according to O'Hagan. One having ordinary skill in the art would have been motivated to do so with the expectation of producing biodegradable microparticles for administration to vertebrates to effect immunization and in the absence of unexpected results, the exclusion of the washing step does not patentably distinguish the invention, which uses 4 liters of water in a cross-flow filtration, over a process that washes the microparticles.

***Response to Arguments***

4. Applicant's arguments filed 1/16/07 have been fully considered but they are not persuasive.

Applicant argues that O'Hagan does not teach or suggest filtration step that would provide bound or unbound detergent.

**Response:**

The claims recite broad category of filtration which applicant argues results in unbound and bound detergent. Thus if a generic filtration process provides bound or unbound detergent, it flows that the O'Hagan's filtration of composition containing particles and detergent would also provide unbound and bound detergent.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period



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will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Blessing Fubara  
Patent Examiner  
Tech. Center 1600

BF

  
MICHAEL G. HARTLEY  
SUPERVISORY PATENT EXAMINER